the protein might be doing. I like to think that this is an example of blue skies research turning out to be practically useful, although it has yet to lead to therapy for this debilitating neurological disorder.

What are the most exciting areas for future research? It is possible to forget that we live in the golden age of biology and will do for some time to come. Genome projects have given us a list of components but told us nothing about how they work to make life. The next century of biomedical research will be required to fully exploit this resource. Nominating areas of future research excitement is almost always a futile exercise because, thank goodness, we are constantly being surprised. This unpredictability is precisely why curiosity-driven research is such a vital part of the future. In spite of the uncertainty, an obvious area to watch closely is the brain. Here ignorance is huge and the possibility of surprising discoveries correspondingly great.

Ambitions? Having presided over my share of transient transfections using permanent cell lines, I have finally come to accept the truism that such cells are biologically eccentric entities with limited relevance to life as we know it. Neurons, on the other hand, are 'real' cells that are huge and can preserve their complex structure and connectivity in the nervous system for decades. As yet we know little about how their molecular biology makes this possible. It was amazing to find recently that mice with severe brain malfunction due to MeCP2-deficiency could be essentially cured by putting the protein back. Like others, we had assumed that such "neurodevelopmental" defects would be irreversible. It looks as though MeCP2 acts as a maintenance factor that fixes gene expression programmes in different types of mature neurons. Now this idea needs testing.

The Wellcome Trust Centre for Cell Biology, School of Biological Sciences, University of Edinburgh, Michael Swann Building, Mayfield Road, Edinburgh EH9 3JR, UK.
E-mail: a.bird@ed.ac.uk

My Word

On learning to write

Mark Ptashne

I learn from Bill Bryson in his fine "*A Short History of Everything*" that obscure scientific writing has a well-established history. Newton wrote impenetrably to keep tourists out; the geologist Hutton, with profound things to say, wrote obscurely, and to his detriment, because he was incapable of writing a coherent English sentence. Is there a third, perhaps more modern, category of obscurantism? Let's face it: day by day molecular biology can be tedious stuff indeed. Surely there must be some better world — one in which we solve meta-problems rather than quotidian ones. The public (including us) wants what we might call a 'leapfrogging': there must be a way, or ways, to describe and deduce in general rather than in particular. In that breathless atmosphere, obscurity can be useful to the writer, ignored or encouraged by editors, embraced by administrators and deep pockets.

Lets put these dark thoughts aside. Most of us, I'll assume, do want to write clearly, but how does one learn to do it? Our brains (some anyway) work in fits and starts — this reminds me of that, that reminds me of this, do you know the joke about Sam, and so on. But standard scientific writing won't allow that to be transferred to the page. Some people think the problem must be tackled on a grand scale: the student is told to present and defend, in writing, an experimental plan to solve an outstanding problem outside his main area of interest. Wow — a job for JBS Haldane, but not for most of us. As a graduate student, I assisted in a course taught by Jim Watson at Harvard. One of Watson's requirements was that each student write a three page paper on something, anything, related to the course. Oh what masterpieces of indirection were produced! And what a valuable lesson it was.

There are some rules that help, I suppose: short sentences, the active voice, as few technical and compound words as possible, and so on. I used to write by hand, read (out loud) into a tape recorder, re-read the typed outcome, throw away, read a page of Nietzsche, and start again. But in my experience these rules and methods are only the starting point, and some rather more 'interactive' instruction is required. Watson applied the following method (at least to me): my finely honed draft was sailed back across the table accompanied by an eyebrow-push-up-grimace and the word: "Unreadable". Reminds me of my all-time most memorable violin lesson. I walked into the home of the Russian virtuoso with whom I was studying and he said, deadpan: "I see you are smiling. Why are you smiling? If I played like you I wouldn't smile."

We call this the boulder-in-the-road teaching method, and it is not so uncommon in music, especially among the great Russians. A friend of mine tells me about her friend who went to study with Heifetz — yes, Jascha Heifetz. The first week he told Heifetz he would play the Sibelius Concerto, and JH said "We'll see about that." The student got through the first page before being sent home "to practice". Upon repeated attempts he never got past the first page until, the last day, JH let him play the whole thing and then said: "It's as I thought: you can't play the Sibelius Concerto. Next." Before being too harsh on Jascha, recall the story about Max Delbrück — the very Max I mentioned in my last communiqué [1]. It is said that Max returned a manuscript, torn to pieces, along with a note that said: "Please switch fields."

Al Hershey didn't bother to tear up my manuscript. I wrote a 20 page paper for him and got it back with most lines crossed out and the occasional phrase circled and marked "Good". So I rewrote and rewrote and it came back with not a mark on the first page! Not a mark on the second! Then the third page: a line through the middle, a penciled-in "START HERE", and

then most lines thereafter crossed out. Madame Auclair, the French violinist, had a gentler approach. Out of central casting, as they say: dark glasses, cigarette dangling, hoarse, accented voice. A friend went for a special violin lesson, and asked whether he might tape record this important event in his life. "Of course, my boy." He played a bit and she said: "Very nice. There are some good things about your playing, very good. Now turn off the tape recorder."

When I am struggling over yet another of my obscurely written drafts I sometimes recall: amateurs play music 'in general'; professionals play each note. And so I present to a tough-minded friend one paragraph — just one — and when that is reported to be transparent I go on to the rest. But even if I have followed the rules I mentioned above, and even if that first paragraph seemed fine at the time, now, in view of what else I have written, that first paragraph might have to go, or be seriously recast. Each paragraph is an experiment — you might not know for some time whether it is any good.

There is a theme here, beautifully expressed by a friend who was going through the agonies of the "just the first paragraph" method in attempting to re-write a book. I hadn't heard from him in a while and began to worry — had I been too tough? — and he wrote: "The only reason I hadn't sent it (the new paragraph) already is that I didn't want to disappoint you. But I realize that the only way you can help me is if I continue to disappoint you. So here it is..." All my teachers, whatever their methods, were trying to help me, and I love them for it. Heifetz I wouldn't be so sure about. Rules are one thing, but in the end communication is all: at the end of a pleasant interview with a fine scientist of foreign extraction she shook my hand and said: "Its been a pleasure talking to me."

Reference

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Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 595, New York, New York 10021, USA.
E-mail: m-ptashne@mskcc.org

Quick guide

RecA

Roberto Galletto and Stephen C. Kowalczykowski

What is RecA protein? The bacterial RecA protein is the founding member of a class of proteins with homologs across all domains of life: RadA in archaea, and Rad51 and Dmc1 in eukaryotes. In *Escherichia coli*, RecA is essential for recombinational repair of DNA breaks, induction of the DNA damage-induced 'SOS' response, and activation of translesion DNA synthesis. The functional form of RecA protein in these processes is the nucleoprotein filament, the structure formed by assembly of RecA protein on DNA (Figure 1), generally single-stranded DNA. During homologous recombination, the RecA nucleoprotein filament catalyzes the pairing and exchange of complementary DNA strands between homologous regions of DNA. In response to DNA damage, the RecA nucleoprotein filament activates the SOS response by catalyzing the auto-cleavage (co-protease activity) of the LexA repressor, leading to derepression of over 40 unlinked genes involved in DNA repair, including the *recA* gene itself. And through both cleavage (of the UmuD subunit) and direct binding, the RecA nucleoprotein filament activates DNA polymerase V ($UmuD'_2C$ protein), a lesion by-pass DNA polymerase, to synthesize DNA at otherwise irreparable lesions, resulting in a mutagenic form of DNA repair known as translesion synthesis.

What is the RecA nucleoprotein filament? The active form of RecA and of all its homologs is the ATP-bound nucleoprotein filament formed on DNA. The protein forms a polymorphic right-handed helix around the DNA with approximately six monomers per turn and a pitch of ~9.5 nm, in which the DNA is extended to about 150% of its B-form length. This quaternary organization is responsible for the catalytic properties of the protein. Formation of the nucleoprotein filament occurs by a mechanism similar to that of other self-associating proteins,

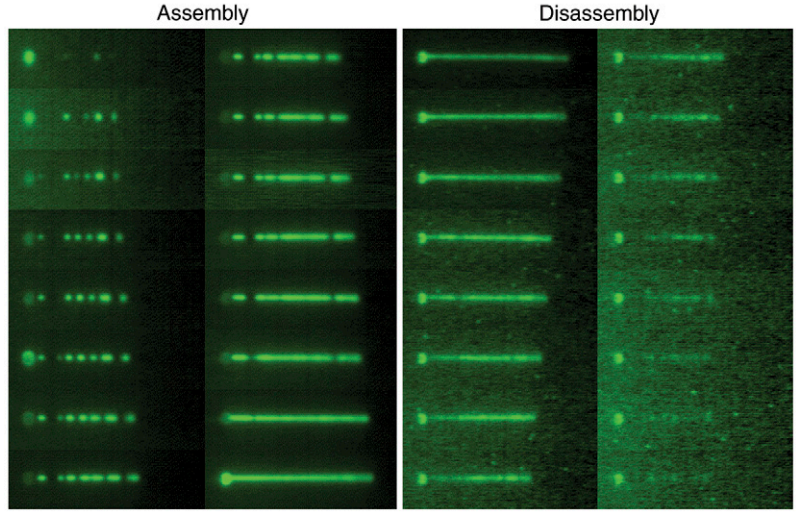

Figure 1. Assembly and disassembly of a RecA nucleoprotein filament formed on an individual double-stranded DNA molecule.

The collage shows the major steps in the entire cycle of RecA nucleoprotein filament assembly and disassembly as visualized by single-molecule detection. The DNA, which is invisible in these images, is bound to a polystyrene bead (leftmost 'spot'). The RecA is fluorescently labeled, permitting visualization of the DNA-bound protein. From top to bottom and left to right, snapshots of RecA assembly from multiple nuclei to generate complete filaments (left-most two columns), followed by images of disassembly promoted by ATP hydrolysis (right-most two columns).